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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,986	07/01/2002	Seishi Nagamori	56972 (71526)	2684

21874 7590 02/03/2009

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EXAMINER	
HORNING, MICHELLE S	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
02/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,986	NAGAMORI, SEISHI	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103-MAINTAINED

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Kawada et al (1998) and Aoki et al (1998).

Kawada et al meets the structural limitation of the bioreactor system. The authors disclose a support system employing a highly functional liver cell line cultured in a radial flow bioreactor and compared the cells to those grown in a conventional monolayer culture (see Summary). The radial flow bioreactor consists of a matrix comprised of porous glass bead microcarriers to which cells attach and proliferate throughout the matrix (see Results). Using the disclosed three-dimensional culture leads to the cell's natural morphology and function. The continuous flow through the matrix generates a beneficial concentration gradient of oxygen and nutrients while preventing excessive shear stresses or build up of waste products (see Introduction). Further, conditions resembling the *in vivo* state can be achieved (see Introduction). See Figures 2 and 3 for a diagram of the system and the 3D morphology of the cells achieved by this system. The authors demonstrate that this bioreactor can maintain highly dense cell cultures in

excess of 1.1 x 10^8 cells/ ml-matrix (see page 114). Page 114 provides the following recitation:

"Three-dimensional culture enables cells to be globe shaped and to come true high density culture because of the good condition of the cells. Another important benefit of the radial flow bioreactor is the ability to scale up. Theoretically, massive cultures can be maintained in bioreactors having volumes of tens of liters."

The authors also note the following on page 113:

"The present study demonstrated that the new reactor device overcomes several of the problems associated with conventional culture systems: (a) short culture lifespan and insufficient cellular function and productivity due to poor culture environment, (b) insufficient cell density, and (c) difficulty to scale-up culture processes". This reference does not teach proliferation of hepatitis C virus or FLC4 cell line (claim 34).

Aoki et al. teach an *in vitro* system that successfully supports the efficient growth of HCV via the FLC4 cell line. Following transfection with RNA, this cell line in particular exhibited very high reporter gene expression with pT7HCVLuc in comparison to the low success rates of various other cell lines (see Abstract). Aoki et al. teach that the combination of the HCV minigene with the FLC4 cell line is "useful to study the virus-cell interaction of HCV infection and other viruses for which there are no efficient in vitro replication systems" (see Introduction).

Thus, it would have been obvious to the ordinary artisan to combine the two teachings above in order to perform a method of proliferating HCV using the FLC4 cell line and the disclosed bioreactor. One would have been motivated to do so in order to

provide optimal culture conditions of the hepatocytes (see Kawada et al) using a particular cell line known to successfully express HCV (Aoki et al). Also, Kawada et al describe the ability of the system to maintain massive cultures and "scale up" as opposed to conventional culture systems (see pages 113 and 114). Combination of the teachings would allow for the artisan to proliferate HCV at a greater scale using maintained massive culture. There would have been a reasonable expectation of success given the authors of the references applied demonstrate either a successful bioreactor or cell line. Of note, it would have been obvious to stop circulation of the culture medium in order to take a test sample (e.g. pH testing or confirm HCV infectivity) and restart the circulation in order to allow for continued proliferation of HCV (see claim 30). Also, it would have been obvious to the ordinary artisan to alter the supply rate of either the medium or oxygen to the cells before, during and after HCV infection of the cells in order to gain optimal results (see claim 31); any modification of the supply (including rate of supply) is considered routine optimization. For these reasons, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 11/18/2008 have been fully considered but they are not persuasive. Applicant emphasizes that the teachings by Kawada provide a continuous flow of media in the bioreactor for maintaining conditions of optimal cell growth of hepatic cells (see page 4, Remarks). Applicant argues that Kawada does not provide any teaching where the flow of media is *not continuous* (see page 5, Remarks).

Applicant also argues that Aoki teaches infection of cell grown in a 12-well plate and media cannot be circulated in a 12-well plate (see page 6, Remarks). Applicant argues that as amended the instant claims are distinct from the teachings of Aoki because Aoki teaches that after addition of the virus, the inocula should be removed after 60 minutes and replaced with fresh media (page 6, Remarks).

The above arguments are not found to be persuasive. Kawada clearly provides a method of using a radial flow bioreactor which allows a cell to maintain its natural morphology and function. Further, Kawada provides that the radial flow bioreactor allows for the scaling up of cultures. Aoki provides a successful method of infecting cells in a 12-well plate. The ordinary artisan would have applied the teachings of Kawada in order to scale up healthy cells in culture and then apply the teachings of Aoki for the successful infection of cells. Amendments to the claims include the following: stopping circulation of the medium for 2 to 10 hours after adding virus, circulating the culture medium without supplying fresh medium for 6 to 48 hours and increasing a supply rate of fresh medium and a supply rate of oxygen to 1.5-fold to 2.5-fold for 30 minutes to 2 hours immediately prior to the addition of HCV to the culture medium. However, the office maintains that it would have been obvious for the ordinary artisan to alter/adjust multiple parameters in order to optimize results and such adjustments for optimization seem to be supported by the instant claims in that circulation is stopped for 2, 3, 4, 5, 6, 7, 8, 9 or 10 hours following the addition of virus, for example. Applicant provides the following recitation: "Aoki teaches that after addition of the virus, the inocula should be removed after 60 minutes and replaced with fresh media""(see Remarks, page 6).

However, given that there is a clear disparity of multiple factors (e.g. volume of medium and cell numbers in a scaled up culture) the two cell cultures taught by Kawada and Aoki, the ordinary artisan would adjust conditions accordingly. For example, a scaled-up culture may require longer incubation durations or different concentrations of virus for infection than a smaller culture in smaller 12-well plate and thus, fresh medium would be supplied at different time points. An increase in the supply rate of fresh medium prior to the addition of HCV may be required in a radial flow bioreactor because a high cell density results in increased cellular debris compared to that of a well of a 12-well plate.

The Office maintains that the instant invention is obvious for the following reasons:

1. The radial flow bioreactor is known to produce healthy cells and scale up hepatic cells (see Kawada);

2. Successful methods of HCV infection are known in culture (see Aoki);

3. The ordinary artisan would have adjusted/altered various conditions (e.g. supply rate of oxygen, medium, incubation times, pH, temperature, viral concentrations) to achieve optimal results in a massive culture as routine experimentation. There is ample motivation to do so and this would have been obvious to the ordinary artisan. See MPEP 2144.05; and

4. It is not clear what makes the claimed invention novel and there is no evidence that the amended method steps are critical to the invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that

any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/
Examiner, Art Unit 1648

/Bruce Campell/

Supervisory Patent Examiner, Art Unit 1648